How Safe Is Universal Hepatitis B Vaccination?

Burton A. Waisbren, Sr., M.D., F.A.C.P.

INTRODUCTION

Universal hepatitis B vaccination of infants in the United States, regardless of risk factors, was first proposed by Margolis and his coworkers of the hepatitis branch of the Center for Disease Control and Prevention in Atlanta, Georgia.[1,2] The concept was endorsed and augmented by West and his coworkers at the Merck Sharpe and Dohme research laboratories in West Point, Pennsylvania.[3] The rationale presented for universal vaccination of infants in the U.S. stemmed from the failure of the current strategies for controlling this disease and not from trials that demonstrated the effectiveness or safety of a universal hepatitis B vaccination program.[4,5] In spite of this, universal hepatitis B vaccination is achieving wide spread acceptance among medical organizations and is being vigorously pursued in many sections of the country.[5,6]

To be presented here are four patterns that raise some concerns about vaccinating all babies in the U.S. with the hepatitis B vaccine. The patterns are as follows: The historical pattern of events that followed the introduction of an antirabies vaccine in the late 1800's and of warnings regarding probable occurrence of vaccine complications given by medical scientists during the past 50 years; the pattern revealed by animal experimentation that showed that viruses and viral particles may cause demyelination and autoimmunity in a variety of species; the pattern of autoimmunity and demyelination that has been caused by the hepatitis B infection, itself; the pattern of clinical reports that reveal that demyelination and autoimmunity have appeared in patients vaccinated with hepatitis B vaccines.

Reasonable steps that might be taken to address the concerns evoked by the above patterns will be discussed.

Postvaccinal Encephalomyelitis and Warnings by Medical Scientists

Postvaccinal encephalomyelitis has been recognized and accepted as a clinical entity since it first occurred after Pasteur's antirabies vaccine was used.[7] At first the encephalomyelitis was thought to be caused by the nervous tissue in which the virus used for the vaccine was grown.[7] However, postvaccinal encephalomyelitis has appeared in patients who received vaccine grown in duck eggs, so it is now thought that the syndrome is caused by something present in the dead virus.[8] Postvaccinal encephalomyelitis has since been observed after a wide variety of vaccinations.

Within the past 30 years representatives of the medical establishment have discussed and warned about neurologic complications of various vaccines.[9-12] Wilson, in his 1967 monograph regarding vaccine complications, pointed out that there are no insurance policies without premiums and that strict attention must be paid to the premiums exacted by each vaccine.[9] Miller, in 1954, discussed the neurologic sequelae of vaccination and the difficulty of these complications being recognized and accepted.[10] Zuckerman, in an article in 1974 in Nature entitled "Hepatitis Vaccine: A note of caution" pointed out that autoimmunity might well follow the hepatitis B vaccinations because the disease, itself, involved autoimmunity.[11] He suggested, "careful assessment of all vaccine effects on the immune system."[11] As late as 1988, Hilleman, who some call the "father" of hepatitis B vaccine, warned "the message from the hypothetical hepatitis B example is that the administration of antigens or monoclonal antibodies that

directly or indirectly raise antibodies that attach to host cell receptors may carry large liabilities even though they might provide a convenient means for preventing viral access to host cells... antibodies attached to cell receptors may invite the same kinds of adverse response that are believed to be responsible for a variety of autoimmune disorders." [12]

Experiments In Animals That Lead To Concerns about the Hepatitis B Vaccine

Experiments done on animals in the past 60 years have yielded data that add to the concerns about present day viral vaccines. These experiments have shown that polypeptide chains of the types found in viruses that are homologous or nearly homologous with myelin can cause demyelination and have shown that viruses, themselves, can cause demyelination.[13]

The experiments started in 1956 when Rivers showed that myelin injected into monkeys caused demyelination.[14] Wakesman expanded these studies and developed an experimental model in which myelin and adjuvant consistently caused demyelinating disease in mice and rabbits.[15] This has been widely accepted as a model for demyelinating diseases in humans and is called experimental allergic encephalomyelitis (EAE).[16] Stohlman found that a DNA virus called JHM could cause demyelination in mice.[17] Oldstone then presented experimental evidence that autoimmunity in humans was caused by polypeptides in viruses that were homologous to those in human tissue.[18] Fujinami and Oldstone produced EAE in rabbits with proteins from hepatitis B virus that had polypeptides in it that were homologous with myelin.[19] Ziegler produced EAE in rabbits with the Swine Flu Vaccine and adjuvants.[20]

Westall and Root-Bernstein presented data that suggested a syndrome they called Multiple-Antigen-Mediated-Autoimmunity (MAMA) could occur in animals and humans.[21] They postulated that the MAMA Syndrome was operative in postvaccinal encephalomyelitis as well as in EAE.[21] Root-Bernstein hypothesized that this syndrome could occur in humans if four conditions were met. The first was demonstrated homology between an antigen and host tissue. The second was the presence simultaneously, of more than one antigen. The third was complementarity between the antigens shown to be present. The fourth was the additional presence of a bacterial adjuvant. As will be discussed later, all of these requirements can be tested for as a possible explanation for post hepatitis B vaccine reactions.

Finally, the HLA patterns of experimental animals has been shown to influence their susceptibility to experimental demyelinating diseases.[22]

Hepatitis B Infection Causes Autoimmunity and Demyelination

Another group of patterns regarding the consideration of universal hepatitis vaccination, without factoring in risk factors that have been largely ignored, are those revealed by the findings that the infection, itself, causes autoimmunity and demyelination. In 1977, London first reported that autoimmune disease was caused by circulating immune complexes caused by viral antibody association.[23] In 1987, Tsukada reported demyelinizing neuropathy associated with the hepatitis B

infection.[24] Discussions and case reports regarding autoimmunity occurring with the hepatitis B infection have been presented by Vento et al and McFarlane et al.[25,26] As early as 1976, Zuckerman cautioned that since autoimmunity is involved in the pathogenesis of hepatitis B infections that it might be augmented by a hepatitis B vaccination.[11]

Reports Of Demyelination and Autoimmunity After Hepatitis B Vaccination

Clinical experiences since the general release of hepatitis B vaccines suggest that clinical counterparts of the animal studies and autoimmunity that occurs after the hepatitis B infection occur after hepatitis B vaccination. The first report of demyelination after the hepatitis B vaccination was that of Ribera and Dutka in 1983. The complication was transient.[27] The authors stated inflammatory polyradiculoneuropathies after both viral diseases and vaccinations have been widely reported.[27] They emphasized the necessity of continued surveillance of the use of hepatitis B vaccine.[27] I have noted seven cases of a neurologic picture resembling multiple sclerosis (MS) after hepatitis B vaccination.[28] In 1987, Fried et al reported uveitis that occurred in a 20-year-old nurse after a booster dose of hepatitis B vaccine.[29] They pointed out that there is a higher than normal level of hepatitis B antibodies in some uveitis patients. They postulated that these antibodies combined with surface antigens in the vaccine could form a disease producing immune complex.[29]

Shaw et al reported a post marketing surveillance study regarding neurologic events after the hepatitis B vaccine in 1988.[30] An estimated 850,000 individuals had received the vaccine by the time of their

study. They found ten cases of Bell's palsy, nine cases of Guillain-Barre Syndrome, five cases of lumbar radiculopathy, three cases of brachial plexus neuropathy, five cases of optic neuritis, and four cases of transverse myelitis. They concluded, on the basis of the controversial epidemiologic methods used to study the Swine Flu epidemic of 1976, that the risk of the vaccine was outweighed by the prophylactic benefits in "high risk groups."[30,31] However, even using these methods, they concluded that the demyelinating disease, Guillain-Barre Syndrome, occurred more often in individuals who had been vaccinated than in the general population.[30] In 1988, Biron et al reported a case of myasthenia gravis that occurred after anesthesia and a hepatitis B vaccination.[32] They postulated that the autoimmune disease was due to the "challenge" to the immune system by the vaccine.[32] In 1989, Goolsby reported a case of erythema nodosum that occurred after recombinant hepatitis B vaccine.[33] In 1991, Herroelen et al reported on two patients who developed symptoms of increasing demyelination after a vaccination of recombinant hepatitis B vaccine.[34] He mentioned that their HLA patterns might be a contributing factor. Seven hundred reports of adverse reactions to the hepatitis B vaccine were sent in to the Vaccine Adverse Events Reporting Systems (VAERS) between October 1990 and September 1991.[35] This system was set up via the National Childhood Vaccine Injury Act of 1986. Sixteen percent of these reports were of damage presumed to be to the myelin of the nervous system. There were 21 cases of facial paralysis and six cases of MS. Eighty-two of the complications occurred in patients who received plasma derived vaccine and 18 occurred in those who received recombinant vaccine.[35] This difference can be explained by the fact that at the time the VAERS were examined, the recombinant vaccine had just come into general use. In 1990, in the World Health Organization Drug Information Bulletin two

cases of optic neuritis and one case of Guillain-Barre Syndrome were reported to be among the 200 reports of adverse reactions that were reported by the Australian National Regulatory Body.[36] One patient had vertigo and diplopia attributed to demyelination eight months after the vaccination.[36]

In 1993, Trevisani et al reported a case of transverse myelitis that followed a recombinant vaccination in an 11 year-old girl.[37] Their arguments for a causal link between the vaccination and the transverse myelitis were the temporal association (21 days), the previous report of Shaw's in which the same complication occurred, and no clinical evidence of any other cause of the disease.[37] They pointed out that transverse myelitis was occasionally found in patients with hepatitis B.[37] This suggested to them that there might be antigenic determinants held in common with the capsular antigen of the hepatitis B vaccine and myelin.[37]

In 1993, Nadler et al reported a case of "classic MS," the prodromal of which appeared 10 days after a recombinant vaccination.[38] They stated that the benefits of the hepatitis B vaccination, among the population for "which it is usually recommended," far out weigh any potential risks.[38] In 1990, there was a report in the British Medical Journal of vasculitis related to the hepatitis B vaccination.[39] It was felt to be due to immune complex disease. In 1993, Brezin et al reported visual loss and eosinophilia after a recombinant hepatitis B vaccine.[40]

In 1995, Kaplanski et al reported a case of central nervous system demyelination that occurred in a 37-year-old man two weeks after receiving the third hepatitis B injection.[41] This patient had the same haplotype as the patient reported by Herroelen.[34] They suggested that the hepatitis B vaccination could potentially induce CNS demyelination in patients with HLA, B7, DR2 haplotype, whether or not these patients have a history of MS.[41]

Vautier and Carty in 1994 reported a case of classic rheumatoid arthritis that followed a hepatitis B vaccination.[42] They brought up the fact that the patient was HLA, DR4 positive which would be consistent with both animal and previous clinical reports regarding complications of the hepatitis B vaccine.[22,33,42] Hassan and Oldham reported two cases of reactive arthritis and Reiter's Syndrome that occurred after a recombinant hepatitis B vaccine.[43] They cite a personal communication from the manufacturer that stated that in 11 cases reported to them of reactive arthritis following recombinant hepatitis B vaccine that six had a recurrence of symptoms after a second vaccination.[43]

In 1995, Tartaglina et al reported a case of postvaccinal myelitis that occurred one month after a hepatitis B vaccination..[44] They suggested that complications of this sort may be under reported because there can be a delay in symptom occurrences.[44] In the case they reported, symptoms did not occur until one month after a single injection of the vaccine. No other cause of the myelitis was shown by a MRI.[44]

DISCUSSION

How might the concerns evoked by the material that has been presented be addressed?

Parents of babies and adolescents who have little chance of being exposed to hepatitis B should be made aware of the potential dangers of the vaccine. A perspective, inclusive, long term follow up study of a large number of individuals who have received the vaccine should be done and the results should be made available to the parents of children who are to be vaccinated. While these admittedly tedious studies are being conducted, databases available through societies such as the Multiple Sclerosis Society might be used to determine if an inordinate number of patients with multiple sclerosis had received a hepatitis B vaccination prior to being diagnosed.

The literally hundreds of individuals who have been reported to VAERS and pharmaceutical companies, who claim to have suffered demyelination and autoimmunity from a hepatitis B vaccine, should be followed up to determine their HLA patterns to ascertain if host factors are partially causative of the complication.[22,33]

A large group of individuals who are to be vaccinated should have before and after determinations by the methods of Zhang, Wucherpfennig and Strominger of the percentage of their T-cells that exhibit antimyelin activity to determine if vaccination does evoke such cells in some individuals with certain HLA patterns.[47,48]

The ability of vaccines when injected with adjuvant into animals to cause EAE should be tested using the methods of Fujinami and Ziegler.[19,20]

The hypothesis and studies of Westall and Root-Bernstein that indicate a multifactorial pathogenesis of postvaccinal encephalomyelitis suggest a series of studies that could be done on vaccines and on patients who developed complications after the hepatitis B vaccination.[21] Hepatitis B vaccine and all other vaccines should be tested for the extent of their polypeptide homology with human tissue.[13,21] If significant homology were to be demonstrated, the offending polypeptides could be removed from the vaccine or synthetic vaccines could be produced without them.[49,50] If such a homology were to be demonstrated, it would fulfill the first requirement for the provocative hypothetical MAMA Syndrome of Westall and Root-Bernstein.[21] The second requirement for the MAMA Syndrome is that multiple antigens are present.[21] These could be tested for by serologic studies for the Epstein-Barr Virus and other viruses that already have been indicted in this syndrome.[21] The third requirement that complementarity between antigens must be demonstrated could be tested for by complementarity studies between the hepatitis B vaccine and other antigens uncovered by the aforementioned serologic tests.[51] The fourth requirement that an adjuvant be present could be tested for by serologically determining whether muramyl peptides are present.[52] These peptides are well established adjuvants and are ubiquitous as part of the cell walls of all bacteria.[52]

The above-mentioned studies might well yield information that would not only make all vaccines safer, but could lead to means to prevent postvaccinal autoimmunity by the methods shown to work in animals by Westall and Root-Bernstein and Norga et al.[53,54]

Finally, it should be emphasized that the concerns voiced above in no way denigrate worldwide programs that are attempting to reduce hepatitis B in populations of extremely high risk, both internationally and in the U.S.[55] Certainly, there should be no abrupt stopping of present vaccination programs in the U.S., but it does seem reasonable to develop an informed consent that discloses to parents the potential dangers of the vaccine. Parents then would be able to intelligently decide whether the risk involved justifies their child receiving the vaccination. This might be particularly reasonable in areas of the U.S. in which the incidence of hepatitis B is very low.

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ABOUT DR. WAISBREN

Burton Waisbren, Sr., M.D., F.A.C.P. is a native Milwaukean who received his B.S. and M.D. degrees at the University of Wisconsin Medical School in Madison, Wisconsin. He served his internship at the Harvard Service at Boston City Hospital. His military service was at the Navy Medical Research Institute, Bethesda, Maryland and the Biological Warfare Center, Camp Dietrick, Maryland. His residency and fellowship was served at the University of Minnesota Hospitals where he was an instructor in the medical school. He received a master's degree in bacterial genetics from the University of Minnesota in 1951. He moved to Milwaukee, his hometown, in 1951 and established a private practice in internal medicine, infectious disease and immunology. At that time, he also headed the infectious disease control unit at the Milwaukee County Hospital. From 1951 to 1969, he was the director of the infectious disease division of first the Marquette Medical School and then the Medical College of Wisconsin. During that time, he was appointed associate clinical professor of medicine. He was the infectious disease consultant of the St. Mary's Hospital Burn Center from 1962 to 1982. He has directed an immunotherapy clinic in Milwaukee since 1973. He has published numerous articles in the medical literature and has authored books on systematic methods of critical care and on medical emergencies.

Dr. Waisbren is board certified by the American Board of Internal Medicine and also is a fellow of the American College of Physicians and the Infectious Disease Society of America. He is a founding member of the Infectious Disease Society of America, the American Burn Association, and the Critical Care Society of America.

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